

WHAT IS CLAIMED IS:

1. A compound comprising at least one alpha helical cyclic peptide, wherein the peptide consists essentially of a sequence of five amino acid residues having a first terminal residue and a second terminal residue that are separated by an intervening sequence of three amino acid residues,
5 and wherein the side chains of the first and second terminal residues are linked to each other, with the proviso that when the compound comprises a single cyclic peptide it is selected from a compound that consists essentially of the single peptide or a compound that comprises the single peptide and a non-peptide moiety or a compound that comprises the single peptide and a combination of a peptide moiety and a non-peptide moiety or a compound that comprises the single peptide and at least one other
10 peptide that comprises at least one amino acid whose side chain has been derivatized and that when the compound comprises two or more cyclic peptides, at least two of these are located immediately adjacent to each other.
2. A compound according to claim 1, wherein an individual cyclic peptide is linked directly or indirectly to a non-peptide moiety.
- 15 3. A compound according to claim 2, wherein the non-peptide moiety is selected from: an aldehyde; a toxin; a drug; a polysaccharide; a nucleotide; an oligonucleotide; a label; an imaging reagent; a hydrocarbon linker that is conjugated to a moiety that provides for attachment to a solid substratum or that provides for ease of separation or purification.
4. A compound according to claim 1, wherein the or each cyclic peptide is a macrocycle
20 formed by consecutively linking at least 18 to 22 atoms, wherein the first and last atoms are bonded to one another to form a ring.
5. A compound according to claim 4, wherein the macrocycle is formed from 19 to 21 atoms
6. A compound according to claim 4, wherein the macrocycle is formed from 20 atoms.
- 25 7. A compound according to claim 1, wherein the first and second terminal residues are selected from alpha amino acid residues.
8. A compound according to claim 7, wherein one of the first and second terminal residues is Lys and the other is Asp.
9. A compound according to claim 7 or claim 8, wherein the resulting macrocycle ring size
30 is 18-22 atoms.
10. A compound according to claim 7 or claim 8, wherein the resulting macrocycle ring size is 20 atoms.
11. A compound according to claim 1, wherein the amino acid side chains of the first and second terminal residues are linked by a covalent bond either directly or through a linker.
- 35 12. A compound according to claim 11, wherein the side chains are covalently linked to one another without an intervening linker.
13. A compound according to claim 11, wherein the side chains are covalently linked to one another by a lactam bridge between a side chain amino group and a side chain carboxylic acid group.

14. A compound according to claim 11, wherein the side chains are covalently linked to one another by a disulfide bond between two side chain thiol groups.

15. A compound according to claim 11, wherein an amine in the side chain of one amino acid residue is reacted with a carboxylic acid in the side chain of a second amino acid residue to form an amide bond or lactam bridge.

16. A compound according to claim 1, wherein one of the first and second terminal residues is selected from L-aspartic acid, L-glutamic acid, D-aspartic acid, D-glutamic acid, L- α -methyl-aspartic acid, L- α -methylglutamic acid, D- α -methylaspartic acid and D- α -methyl-glutamic acid, and the other is selected from L-lysine, L-ornithine, D-lysine, D-ornithine, L- α -methyllysine, D- α -methyllysine, L- α -methylornithine and D- α -methylornithine.

17. A compound according to claim 16, wherein an amide bond is formed between the first and second terminal residues by reaction of an L-aspartic acid or L-glutamic acid with an L-lysine or L-ornithine.

18. A compound according to claim 1, wherein the amino acid residues in the sequence of the peptide are selected from D- or L- α -amino acids.

19. A compound according to claim 1, wherein the amino acid residues in the sequence of the peptide are selected from L- α -amino acids.

20. A compound according to claim 1, which comprises two or three consecutive alpha helical cyclic pentapeptides.

21. A compound according to claim 1, which comprises two consecutive alpha helical cyclic pentapeptides spaced from a third alpha helical cyclic pentapeptide by about 1, 2, 5, 8 or 9 natural or unnatural helix-forming amino acid residues.

22. A compound according to claim 1, which comprises three consecutive alpha helical cyclic pentapeptides spaced from a fourth alpha helical cyclic pentapeptide by about 0, 3, 4, 6 or 7 natural or unnatural helix-forming amino acid residues.

23. A compound according to claim 1, which comprises three consecutive alpha helical cyclic pentapeptides spaced from a fourth alpha helical cyclic pentapeptide by about 1, 2, 5, 6 or 9 natural or unnatural helix-forming amino acid residues.

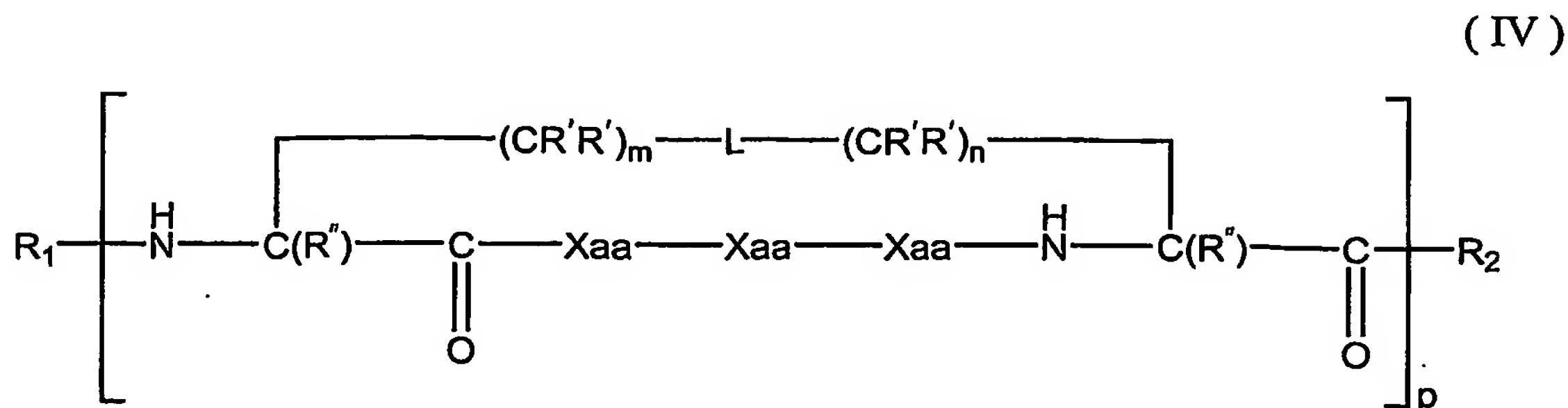
24. A compound according to claim 1, which comprises four consecutive alpha helical cyclic pentapeptides spaced from a fifth alpha helical cyclic pentapeptide by about 1, 2 or 3 natural or unnatural helix-forming amino acid residues.

25. A compound according to claim 1, which comprises five consecutive alpha helical cyclic pentapeptides spaced from a sixth alpha helical cyclic pentapeptide by about 2, 7, 12 or 17 natural or unnatural helix-forming amino acid residues.

26. A compound according to claim 1, which comprises at least one cyclic peptide and at least 1 amino acid residue adjacent thereto.

27. A compound according to claim 26, which comprises a single cyclic peptide and another amino acid residue located immediately upstream or downstream thereof.

28. A compound according to claim 1, which has a plurality of alpha helical cyclic pentapeptide sequences and is represented by formula (IV):



wherein each Xaa is independently selected from any amino acid residue;

R₁ is selected from H, an N-terminal capping group, a peptide of 1 to 20 amino acid residues optionally capped by an N-terminal capping group, a non-peptidic group or a group that mimics an amino acid side chain;

R₂ is selected from H, a C-terminal capping group, a peptide of 1 to 20 amino acids optionally capped by a C-terminal capping group, a group that mimics an amino acid side chain or a group that activates the terminal carboxylic acid carbonyl group to nucleophilic substitution;

each R' and R'' are independently selected from H, C₁-C₁₀alkyl, C₂-C₁₀alkenyl, C₂-C₁₀alkynyl, C₃-C₁₀cylcoalkyl, C₅-C₁₀cycloalkenyl, -OH, -OC₁-C₁₀alkyl, -NH₂, -NH(C₁-C₁₀alkyl), -N(C₁-C₁₀alkyl)₂, C₆-C₁₀aryl, C₃-C₁₀heterocyclyl, C₅-C₁₀heteroaryl and halo;

L is selected from $-\text{NH}-\text{C}(\text{O})-$, $-\text{C}(\text{O})-\text{NH}-$, $-\text{S}-\text{S}-$, $-\text{CH}(\text{OH})\text{CH}_2-$, $\text{CH}_2\text{CH}(\text{OH})-$, $-\text{CH}=\text{CH}-$, $-\text{CH}_2-\text{CH}_2-$, $-\text{NH}-\text{CH}_2-$, $-\text{CH}_2-\text{NH}-$, $-\text{CH}_2-\text{S}-$, $-\text{S}-\text{CH}_2-$, $-\text{C}(\text{O})-\text{CH}_2-$, $-\text{CH}_2-\text{C}(\text{O})-$, $-\text{S}(\text{O})_i-\text{NH}-$, $-\text{NH}-\text{S}(\text{O})_i-$, $\text{CH}_2-\text{P}(=\text{O})(\text{OH})-$ and $-\text{P}(=\text{O})(\text{OH})-\text{CH}_2-$;

m is an integer from 1 to 4,

n is an integer from 1 to 4, and

t is 0, 1 or 2,

wherein $m + n = 4, 5$ or 6 and wherein when m is 2 , n is not 3 and when m is 3 , n is not 2 ;
and

p is an integer from 2 to 12; with the proviso that bicyclo (Lys¹³ – Asp¹⁷, Lys¹⁸ – Asp²²) [Ala¹, Nlc⁸, Lys¹⁸, Asp²², Leu²⁷] hPTH (1-31) NH₂ is excluded.

29. A compound according to claim 1, which has a plurality of alpha helical cyclic pentapeptide sequences and is represented by formula (V):



wherein each 1,5-cyclo(Zaa-XaaXaaXaa-Yaa) is independently selected from:

cyclo-1,5-KxaaXaaXaaD, [SEQ ID NO: 32]

cyclo-1,5-DxaaXaaXaaK, [SEQ ID NO: 33]

cyclo-1,5-KxaaXaaXaaE, [SEQ ID NO: 34]

cyclo-1,5-ExaaXaaXaaK, [SEQ ID NO: 35]

cyclo-1,5-OxaaXaaXaaD, [SEQ ID NO: 36] and

cyclo-1,5-DxaaXaaXaaO, [SEQ ID NO: 37]

q is an integer from 2 to 12 and R₁ and R₂ are as defined above.

30. A compound according to claim 29, wherein individual pentapeptide sequences are different.

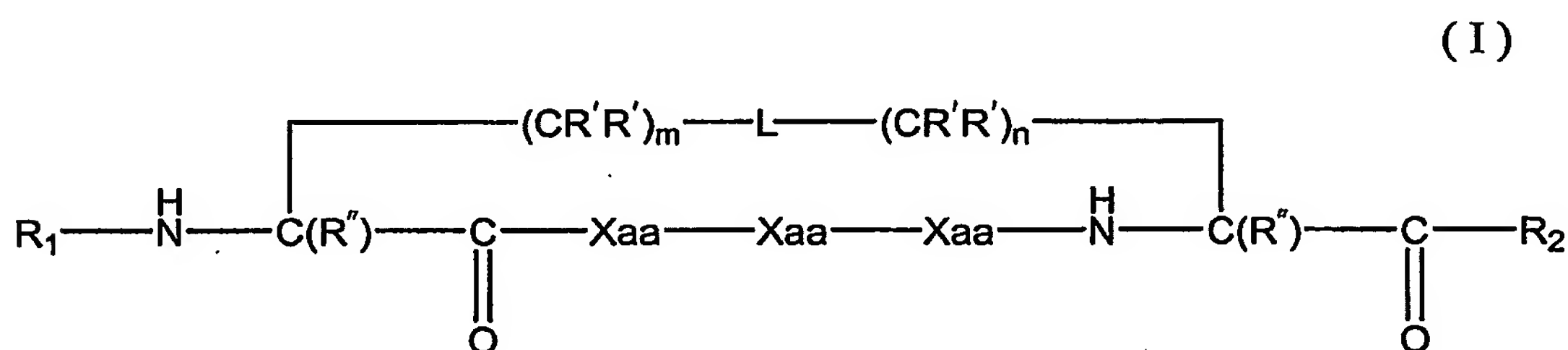
31. A compound according to claim 29, wherein individual pentapeptide sequences in the peptide are the same.

32. A compound according to claim 29, selected from:

cyclo(1-5, 6-10)-Ac-[KARADKARAD]-NH₂ [SEQ ID NO: 46]; and

cyclo(1-5, 6-10, 11-15)-Ac-[KARADKARADKARAD]-NH₂ [SEQ ID NO: 47].

33. A compound having the formula (I):



wherein each Xaa is independently selected from any amino acid residue;

R₁ is selected from H, an N-terminal capping group, a non-peptidic group or a group that mimics an amino acid side chain;

R_2 is selected from H, a C-terminal capping group, a group that mimics an amino acid side chain or a group that activates the terminal carboxylic acid carbonyl group to nucleophilic substitution;

each R' and R'' are independently selected from H, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 -

5 C_{10} alkynyl, C_3 - C_{10} cylcoalkyl, C_5 - C_{10} cycloalkenyl, -OH, -OC $_1$ - C_{10} alkyl, -NH $_2$, -NH(C_1 - C_{10} alkyl), -N(C_1 - C_{10} alkyl) $_2$, C_6 - C_{12} aryl, C_3 - C_{10} heterocyclyl, C_5 - C_{10} heteroaryl and halo;

L is selected from -NH-C(O)-, -C(O)-NH-, -S-S-, -CH(OH)CH $_2$ -, CH $_2$ CH(OH)-, -CH=CH-, -CH $_2$ -CH $_2$ -, -NH-CH $_2$ -, -CH $_2$ -NH-, -CH $_2$ -S-, -S-CH $_2$ -, -C(O)-CH $_2$ -, -CH $_2$ -C(O)-, -S(O) $_t$ -NH-, -NH-S(O) $_t$ -, CH $_2$ -P(=O)(OH)- and -P(=O)(OH)-CH $_2$ -;

10 m is an integer from 1 to 4,

n is an integer from 1 to 4, and

t is 0, 1 or 2,

wherein $m + n = 4, 5$ or 6 and wherein when m is 2 , n is not 3 and when m is 3 , n is not 2 .

34. A compound according to claim 33, wherein R_1 is selected from H; an N-terminal
15 capping group that stabilizes the terminus of a helix; a non-peptidic group; or a mimic of an amino acid side chain.

35. A compound according to claim 34, wherein the N-terminal capping group is selected from acyl and N-succinate.

36. A compound according to claim 34, wherein the mimic of the amino acid side chain is
20 selected from any natural or unnatural amino acid side chain that is attached to the N-terminal amino group of the peptide through a carbonyl group derived from a carboxylic acid by formation of an amide bond.

37. A compound according to claim 34, wherein the mimic of the amino acid side chain is selected from: CH $_3$ CH $_2$ C(O)(CH $_2$) $_u$ C(O)-, NH $_2$ (NH=)CNHC(O)(CH $_2$) $_u$ C(O)-,
25 H $_2$ NC(O)(CH $_2$) $_2$ C(O)(CH $_2$) $_u$ C(O)-, HOC(O)(CH $_2$) $_2$ C(O)(CH $_2$) $_u$ C(O)-, HS(CH $_2$) $_2$ C(O)(CH $_2$) $_u$ C(O)-, H $_2$ NC(O)(CH $_2$) $_3$ C(O)(CH $_2$) $_u$ C(O)-, HOC(O)(CH $_2$) $_2$ C(O)(CH $_2$) $_u$ C(O)-, (4-imidazolyl)(CH $_2$)C(O)(CH $_2$) $_u$ C(O)-, CH $_3$ CH $_2$ CH(CH $_3$)CH $_2$ C(O)(CH $_2$) $_u$ C(O)-, (CH $_3$) $_2$ CH(CH $_2$) $_2$ C(O)(CH $_2$) $_u$ C(O)-, H $_2$ N(CH $_2$) $_5$ C(O)(CH $_2$) $_u$ C(O)-, CH $_3$ S(CH $_2$) $_3$ C(O)(CH $_2$) $_u$ C(O)-, Ph(CH $_2$) $_2$ C(O)(CH $_2$) $_u$ C(O)-, Ph(CH $_2$) $_4$ C(O)(CH $_2$) $_u$ C(O)-, HO(CH $_2$) $_2$ C(O)(CH $_2$) $_u$ C(O)-,
30 HOCH(CH $_3$)CH $_2$ C(O)(CH $_2$) $_u$ C(O)-, (3-indolyl)(CH $_2$) $_2$ (CH $_2$) $_u$ C(O)-, (4-hydroxyphenyl)(CH $_2$) $_2$ C(O)(CH $_2$) $_u$ C(O)-, (4-hydroxyphenyl)(CH $_2$) $_3$ C(O)(CH $_2$) $_u$ C(O)-, (CH $_3$) $_2$ CHCH $_2$ C(O)(CH $_2$) $_u$ C(O)-, CH $_3$ CH $_2$ CH $_2$ C(O)(CH $_2$) $_u$ C(O)-, C $_6$ H $_{10}$ CH $_2$ C(O)(CH $_2$) $_u$ C(O)-, C $_5$ H $_8$ CH $_2$ C(O)(CH $_2$) $_u$ C(O)-, CH $_3$ C(O)(CH $_2$) $_u$ C(O)-, CH $_3$ (CH $_2$) $_4$ C(O)(CH $_2$) $_u$ C(O)-, CH $_3$ (CH $_2$) $_5$ C(O)(CH $_2$) $_u$ C(O)-, HOC(O)CH $_2$ C(O)(CH $_2$) $_u$ C(O)-, HS(CH $_2$)C(O)(CH $_2$) $_u$ C(O)-,
35 H $_2$ N(CH $_2$) $_4$ C(O)(CH $_2$) $_u$ C(O)- and HOCH $_2$ C(O)(CH $_2$) $_u$ C(O)- wherein u is 0 or an integer from 1 to 10 .

38. A compound according to claim 34, wherein the non-peptidic groups enhance the stability, bioavailability or activity of the peptides.

39. A compound according to claim 34, wherein the non-peptidic groups is selected from: hydrophobic groups; groups which stabilize or mimic alpha-helices, groups which mimic the secondary structure of peptides; groups which improve bioavailability; and groups which are recognized by transport receptors to allow or improve transport of the peptides to the site of activity.

40. A compound according to claim 33, wherein R_2 is selected from: H; a C-terminal capping group that stabilizes the terminus of a helix; a peptide of 1, 2, 3, 4 or 5 amino acid residues optionally capped with a C-terminal capping group that stabilizes the terminus of a helix; a mimic of an amino acid side chain; or a group which activates the terminal carboxylic acid carbonyl group to nucleophilic substitution.

41. A compound according to claim 40, wherein the C-terminal capping group is NH_2 .

42. A compound according to claim 40, wherein the mimic of the amino acid side chain is any common or unnatural amino acid side chain that is attached to the C-terminal carbonyl group of the peptide through an amine group by formation of an amide bond.

43. A compound according to claim 40, wherein the mimics of the amino acid side chain is selected from: $-NH(CH_2)_uNHCH_2CH_3$, $-NH(CH_2)_uNH(CH_2)_4NHC(=NH)NH_2$, $-NH(CH_2)_uNH(CH_2)_2C(O)NH_2$, $-NH(CH_2)_uNH(CH_2)_2CO_2H$, $-NH(CH_2)_uNH(CH_2)_2SH$, $-NH(CH_2)_uNH(CH_2)_3C(O)NH_2$, $-NH(CH_2)_uNH(CH_2)_3CO_2H$, $-NH(CH_2)_uNH(CH_2)_2(4\text{-imidazolyl})$, $-NH(CH_2)_uNHCH_2CH(CH_3)CH_2CH_3$, $-NH(CH_2)_uNH(CH_2)_2CH(CH_3)_2$, $-NH(CH_2)_uNH(CH_2)_5NH_2$, $-NH(CH_2)_uNH(CH_3)_3SCH_3$, $-NH(CH_2)_uNH(CH_2)_2(3\text{-indolyl})$, $-NH(CH_2)_uNH(CH_2)_2(4\text{-hydroxyphenyl})$, $-NH(CH_2)_uNH(CH_2)_3(4\text{-hydroxyphenyl})$, $-NH(CH_2)_uNH-CH_2CH(CH_3)_2$, $-NH(CH_2)_uNHCH_2CH_2CH_3$, $-NH(CH_2)_uNHCH_2C_6H_{10}$, $-NH(CH_2)_uNHCH_2C_5H_8$, $-NH(CH_2)_uNHCH_3$, $-NH(CH_2)_uNH(CH_2)_4CH_3$, $-NH(CH_2)_uNH(CH_2)_5CH_3$, $-NH(CH_2)_uNHCH_2CO_2H$, $-NH(CH_2)_uNHCH_2SH$, $-NH(CH_2)_uNH(CH_2)_2OH$, $-NH(CH_2)_uNH(CH_2)_5NH_2$ and $-NH(CH_2)_uNHCH_2OH$; wherein u is 0 or an integer from 1 to 10.

44. A compound according to claim 40, wherein the group, which activates the C-terminal carboxylic carbonyl group to nucleophilic substitution, converts the C-terminal carboxylic acid to a group selected from an acid chloride, an acid anhydride, an acyl azide, an O-acylisourea, a phosphonium derivative or an activated ester.

45. A compound according to claim 40, wherein the non-peptidic group enhances the stability and circulating time, or decrease immunogenicity, or increase solubility, bioavailability or activity of the peptides.

46. A compound according to claim 34, wherein the non-peptidic group is selected from: hydrophobic groups; groups which stabilize or mimic alpha-helices; groups which mimic the secondary structure of peptides; groups which improve bioavailability; groups that are recognized by transport receptors to allow or improve transport of the peptide(s) to the site of activity.

47. A compound according to claim 33, wherein each R' is selected from H, CH_3 , CH_2CH_3 , vinyl, OH, OCH_3 , NH_2 , $NH(CH_3)$, $N(CH_3)_2$, phenyl, F or Cl.

48. A compound according to claim 33, wherein each R" is selected from H, CH₃, CH₂CH₃ or vinyl.

49. A compound according to claim 33, wherein m is 1 and n is 3 or 4, m is 2 and n is 4, m is 3 and n is 1 or m is 4 and n is 1 or 2.

5 50. A compound according to claim 33, wherein each Xaa is any amino acid residue selected to mimic the amino acid residues in a known alpha helical peptide of interest or to prepare an unknown peptide having new properties.

51. A compound according to claim 33, wherein an individual Xaa is the same or different as another Xaa .

10 52. A compound according to claim 33, wherein an individual Xaa is selected from a D- or L- alpha amino acid residue.

53. A compound according to claim 33, wherein the compound of formula (I) has at least one Xaa which is a D- or L- alpha amino acid residue that is favorable to helix formation.

15 54. A compound according to claim 33, wherein 2 or 3 of Xaa are D- or L- alpha amino acid residues that are favorable to helix formation.

55. A compound according to claim 54, wherein the D- or L- alpha amino acid residues are selected from alanine, arginine, lysine, methionine, leucine, glutamic acid, glutamine, cysteine, isoleucine, phenylalanine, tyrosine, tryptophan, histidine and aspartic acid.

56. A compound according to claim 33, wherein L is -NH-C(O)- or -C(O)-NH-.

20 57. A compound according to claim 33, selected from: Ac-cyclo-1,5-[KXaaXaaXaaD]-NH₂ [SEQ ID NO. 1]; Ac-cyclo-1,5-[DXaaXaaXaaK]-NH₂, [SEQ ID NO. 2]; Ac-cyclo-1,5-[KXaaXaaXaaE]-NH₂, [SEQ ID NO. 3]; Ac-cyclo-1,5-[EXaaXaaXaaK]-NH₂, [SEQ ID NO. 4]; Ac-cyclo-1,5-[OXaaXaaXaaD]-NH₂, [SEQ ID NO. 5]; Ac-cyclo-1,5-[DXaaXaaXaaO]-NH₂, [SEQ ID NO. 6]; and Ac-Xaa-cyclo-2,6-[KXaaXaaXaaD]-NH₂, [SEQ ID NO. 7].

25 58. A compound according to claim 33, selected from:

Ac-(cyclo-1,5)-[KARAD]-NH₂, [SEQ ID NO. 8];

Ac-(cyclo-1,5)-[DARAK]-NH₂, [SEQ ID NO. 9];

Ac-(cyclo-1,5)-[KARAE]-NH₂, [SEQ ID NO. 10];

Ac-(cyclo-1,5)-[EARAK]-NH₂, [SEQ ID NO. 11];

30 Ac-(cyclo-1,5)-[OARAD]-NH₂, [SEQ ID NO. 12];

Ac-(cyclo-1,5)-[DARAO]-NH₂, [SEQ ID NO. 13];

Ac-[KARAD]-NH₂, [SEQ ID NO. 14];

AcR-cyclo-2,6-[KLLLD]-NH₂, [SEQ ID NO. 15];

AcR-cyclo-2,6-[KLALD]-NH₂, [SEQ ID NO. 16];

35 AcR-cyclo-2,6-[KLFAD]-NH₂, [SEQ ID NO. 17];

Ac-(cyclo-1,5)-[OARAE]-NH₂, [SEQ ID NO. 18];

Ac-(cyclo-1,5)-[EARAO]-NH₂, [SEQ ID NO. 19];

Ac-(cyclo-1,5)-[KARAD]-OH, [SEQ ID NO. 20];

H-(cyclo-1,5)-[KARAD]-NH₂, [SEQ ID NO. 21];

H-(cyclo-1,5)-[KARAD]-OH, [SEQ ID NO. 22];

Ac-(cyclo-2,6)-R[KAAAD]-NH₂, [SEQ ID NO. 23];

Ac-(cyclo-2,6)-R[KALAD]-NH₂, [SEQ ID NO. 24];

5 Ac-(cyclo-2,6)-R[KAMAD]-NH₂, [SEQ ID NO. 25];

Ac-(cyclo-2,6)-R[KAQAD]-NH₂, [SEQ ID NO. 26];

Ac-(cyclo-2,6)-R[KAFAD]-NH₂, [SEQ ID NO. 27];

Ac-(cyclo-2,6)-R[KAGAD]-NH₂, [SEQ ID NO. 28];

Ac-(cyclo-2,6)-R[KGSAD]-NH₂, [SEQ ID NO. 29];

10 Ac-(cyclo-2,6)-R[KSSSD]-NH₂, [SEQ ID NO. 30]; and

Ac-(cyclo-2,6)-R[KGGGD]-NH₂, [SEQ ID NO. 31]

59. A method for constructing a constrained helical peptide, the method comprising: (1) synthesizing a peptide, wherein the peptide comprises a sequence of five amino acid residues having a first terminal residue and a second terminal residue that are separated by an intervening sequence of
15 three amino acid residues, and wherein the individual side chains of the first and second terminal residues are linkable to each other; and (2) cyclizing the peptide by linking the side chain of the first terminal residue with the side chain of the second terminal residue, thereby yielding an alpha helical cyclic peptide.

60. A method according to claim 59, wherein the first terminal residue has a side chain
20 containing an amide bond-forming substituent and the second terminal residue has a side chain containing a functional group capable of forming an amide linkage with the side chain amide bond-forming substituent of the first terminal residue and the peptide is cyclized by reacting the side chain amide bond-forming substituent of the first terminal residue with the functional group of the second terminal residue to form an amide bond linkage, thereby yielding an alpha helical cyclic peptide.

25 61. A method according to claim 59, wherein in step (1) the reactive groups on the side chains, including the amide forming substituents, are protected by a protecting group.

62. A method according to claim 61, wherein the reactive groups on the side chains, including the amide forming substituents, are deprotected prior to cyclization.

30 63. A method according to claim 59, wherein step (2) comprises activating the carboxylic acid to nucleophilic attack by forming an acyloxyphosphonium or uronium derivative of the carboxylic acid.

64. A method of producing a mimic of an alpha helical binding determinant, comprising: providing a protein of interest that comprises an alpha helical domain that interacts with a ligand; identifying a candidate binding determinant situated within a sequence of 3 or more contiguous amino
35 acid residues in the helical binding domain; and selecting a first residue and a second residue in the sequence (designated *i* and *i*+4), which are separated by an intervening sequence of 3 amino acid residues, and which do not do not interact substantially with the ligand, for linkage to each other.

65. A method according to claim 64, wherein the binding determinant is identified using mutagenesis.

66. A method according to claim 64, further comprising synthesizing a peptide that comprises the first and second residues and the intervening sequence and linking the side chains of the first and
5 second residues.

67. A method according to claim 64, further comprising detecting binding of the peptide to the ligand.

68. Use of an alpha helical cyclic peptide, wherein the peptide comprises a sequence of five amino acid residues having a first terminal residue and a second terminal residue that are separated by
10 an intervening sequence of three amino acid residues, and wherein the side chains of the first and second terminal residues are linked to each other, as a scaffold for presenting the side chains of at least some of the five amino acid residues in a conformation that is analogous to the conformation of amino acid side chains of at least a portion of an alpha helical domain of a known protein.

69. A use according to claim 68, wherein the side chains of at least 1 or 2 or all 3 of the
15 intervening amino acid residues are so analogously presented.

70. A use according to claim 68, wherein at least part of the conformationally constrained secondary structure defined by the five amino acid residues mimics a member of a ligand-receptor binding pair.

71. A use according to claim 70, wherein the ligand-receptor binding pair is selected from
20 protein-DNA binding partners, protein-RNA binding partners; protein-protein binding partners and nuclear coactivators; and nuclear receptors.

72. Use of a conformationally constrained peptide having a plurality of alpha helical pentapeptide sequences, wherein the pentapeptide sequences each comprising a sequence of five amino acid residues having a first terminal residue and a second terminal residue that are separated by
25 an intervening sequence of three amino acid residues, and wherein the side chains of the first and second terminal residues are linked to each other, as a scaffold for presenting the side chains of at least some of the amino acid residues of the pentapeptide sequences in a configuration that is analogous to the configuration of amino acid side chains of at least a portion of an alpha helical domain of a known protein.

73. A use according to claim 72, wherein the side chains of at least 1 or 2 or all 3 of the
30 intervening amino acid residues of each pentapeptide sequence are so analogously presented.

74. A use according to claim 72, wherein at least part of the conformationally constrained secondary structure defined by the pentapeptide sequences mimics a member of a ligand-receptor binding pair.

75. A use according to claim 72, wherein some or all of the pentapeptides are located
35 adjacent to one another.

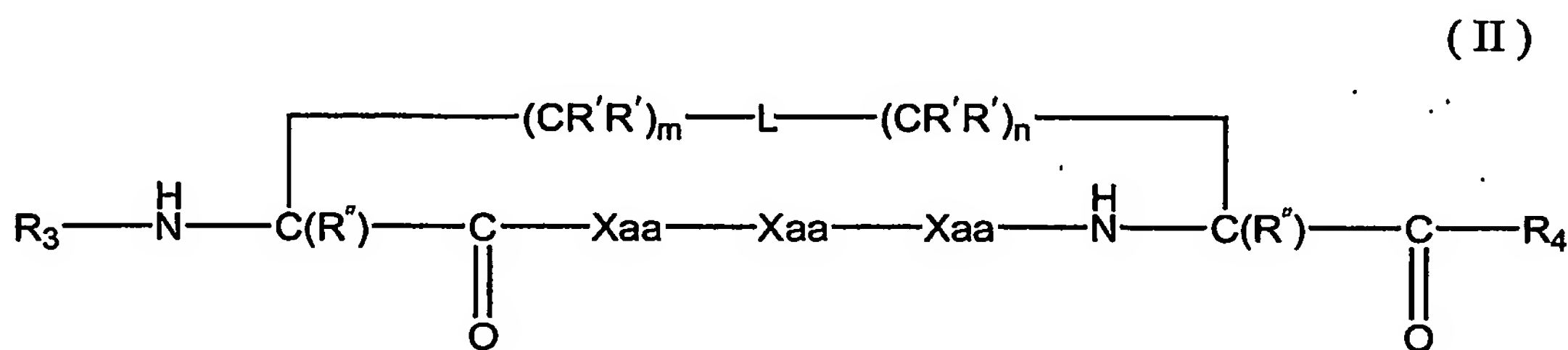
76. A use according to claim 72, wherein at least one of the pentapeptides is spaced from a pair of adjacent pentapeptides.

77. A use according to claim 72, wherein the conformationally constrained peptides are designed to mimic epitopes in proteins and are used to selectively raise polyclonal or monoclonal antibodies against such individual epitopes.

78. A use according to claim 77, wherein the peptides are conjugated to carriers known to be
5 immunogenic in a species to be immunized.

79. Use of at least one alpha helical cyclic peptide, wherein the peptide comprises a sequence of five amino acid residues having a first terminal residue and a second terminal residue that are separated by an intervening sequence of three amino acid residues, and wherein the side chains of the first and second terminal residues are linked to each other, as a macrocyclic module for incorporation into a non-peptidic molecular structure, or for constructing a multi-macrocyclic structure that mimics multiple turns of an alpha helix.

80. A use according to claim 79, wherein the macrocyclic module has the formula (II):



wherein each Xaa is independently selected from any amino acid;

each R' and R'' are independently selected from H, C₁-C₁₀alkyl, C₂-C₁₀alkenyl, C₂-C₁₀alkynyl, C₃-C₁₀cylcoalkyl, C₅-C₁₀cycloalkenyl, -OH, -OC₁-C₁₀alkyl, -NH₂, -NH(C₁-C₁₀alkyl), -N(C₁-C₁₀alkyl)₂, C₆-C₁₀aryl, C₃-C₁₀heterocyclyl, C₅-C₁₀heteroaryl and halo;

L is selected from $-\text{NH}-\text{C}(\text{O})-$, $-\text{C}(\text{O})-\text{NH}-$, $-\text{S}-\text{S}-$, $-\text{CH}(\text{OH})\text{CH}_2-$, $\text{CH}_2\text{CH}(\text{OH})-$, $-\text{CH}=\text{CH}-$, $-\text{CH}_2-\text{CH}_2-$, $-\text{NH}-\text{CH}_2-$, $-\text{CH}_2-\text{NH}-$, $-\text{CH}_2-\text{S}-$, $-\text{S}-\text{CH}_2-$, $-\text{C}(\text{O})-\text{CH}_2-$, $-\text{CH}_2-\text{C}(\text{O})-$, $-\text{S}(\text{O})_t-\text{NH}-$, $-\text{NH}-\text{S}(\text{O})_t-$, $\text{CH}_2-\text{P}(=\text{O})(\text{OH})-$ and $-\text{P}(=\text{O})(\text{OH})-\text{CH}_2-$;

R₃ is selected from H, an N-capping group or a mimic of an amino acid side chain.

R₄ is selected from H, a C-terminal capping group, a mimic of an amino acid side chain or a group which activates the terminal carboxylic acid carbonyl group to nucleophilic substitution;

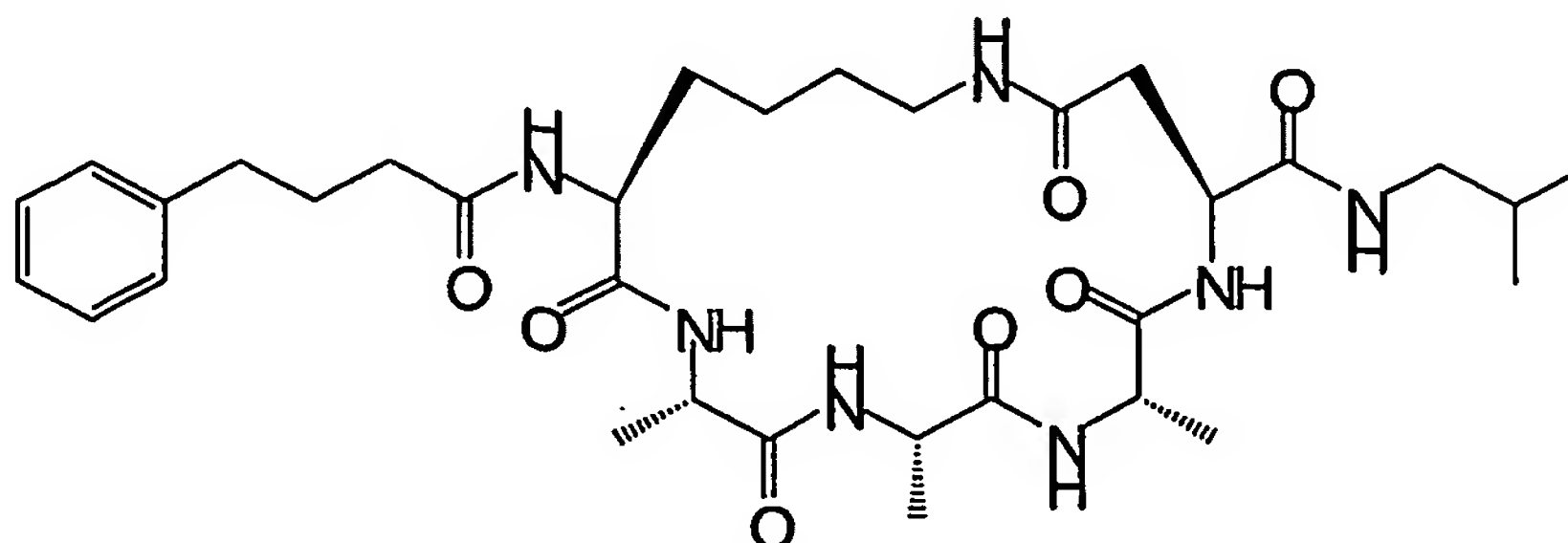
m is an integer from 1 to 4,

n is an integer from 1 to 4, and

t is 0, 1 or 2,

wherein $m + n = 4, 5$ or 6 and wherein when m is 2 , n is not 3 and when m is 3 , n is not 2 .

81. A use according to claim 79, wherein the macrocyclic module has the formula (III):



(III)

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82. A composition comprising a compound according to any one of claims 1 to 51 and a pharmaceutically acceptable carrier, diluent or adjuvant.

83. Use of a compound according to any one of claims 1 to 58 in the manufacture of a medicament for treating or preventing a disease or condition associated with a ligand-receptor interaction that is mediated at least in part by an alpha helical domain present in the ligand or the receptor.

84. A method for treating or preventing a disease or condition associated with a ligand-receptor interaction that is mediated at least in part by an alpha helical domain present in the ligand or the receptor, comprising administering an effective amount of a compound comprising at least one alpha helical cyclic peptide, wherein each peptide comprises a sequence of five amino acid residues having a first terminal residue and a second terminal residue that are separated by an intervening sequence of three amino acid residues, and wherein the side chains of the first and second terminal residues are linked to each other and wherein the side chains of at least some of the amino acid residues of the or each peptide are in a (three-dimensional) configuration that is analogous to the configuration of amino acid side chains of at least a portion of the alpha helical domain of the ligand or the receptor.

85. A method according to claim 84, wherein the disease or condition is related to an aberration in DNA transcription, RNA reverse transcription, transcriptional antitermination, apoptosis regulation, tumor suppression, calcium homeostasis, pain transmission, memory, lipid metabolism, cholesterol homeostasis or stress response or to anxiety, appetite, alcohol withdrawal, opiate withdrawal or epilepsy.

86. A method according to claim 85, wherein the disease or condition is related to aberrant apoptosis regulation or tumor suppression.

87. A method according to claim 86, wherein the compound is selected from a BH3 domain mimetic or a p53 tumor suppressor mimetic.

88. A method according to claim 875, wherein the BH3 domain mimetic is selected from cyclo(2-6,7-11)-Y[KRELD][KMADD]F [SEQ ID NO: 57], cyclo(2-6,7-11)-V[KRQLD][KIADD]I [SEQ ID NO: 58], cyclo(2-6,7-11)-I[KAQED][KVADD]M [SEQ ID NO: 59], cyclo(2-6,7-11)-I[KAQED][KIADD]F [SEQ ID NO: 60], cyclo(2-6,7-11)-3-(4-hydroxyphenyl)-propionyl[KRELD][KMADD]-phenethylamide [SEQ ID NO: 61], cyclo(2-6,7-11)-iso-valeroyl[KRQLD][KIADD]2-methylbutylamide [SEQ ID NO: 62], cyclo(2-6,7-11)-3-methylpentanoyl-[KAQED][KVADD]-3-methylsulfanyl-propylamide [SEQ ID NO: 63], cyclo(2-6,7-11)-3-methylpentanoyl-[KAQED][KIADD]-phenethylamide [SEQ ID NO: 64], Cyclo(3,7)-LR[KMADD]F [SEQ ID NO: 65], Cyclo(3,7)-LA[KIADD]I [SEQ ID NO: 66], Cyclo(3,7)-LA[KVADD]I [SEQ ID NO: 67], Cyclo(3,7)-LA[KIADD]F [SEQ ID NO: 68], Cyclo(2,6)-7-methyl octanoyl-[KMADD]-Phenethylamide [SEQ ID NO: 69], Cyclo(2,6)-7-methyl octanoyl-[KIADD]-2-methylbutylamide [SEQ ID NO: 70], Cyclo(2,6)-7-methyl octanoyl-[KVADD]-2-methylbutylamide [SEQ ID NO: 71] and Cyclo(2,6)-7-methyl octanoyl-[KMADD]-Phenethylamide [SEQ ID NO: 72].

89. A method according to claim 87, wherein the p53 tumor suppressor mimetic is selected from Cyclo(3,7)-FM[K(Pmp)(6ClW)ED]L [SEQ ID NO: 73], Cyclo(3,7)-3-Phenylpropanoyl-M[K(Pmp)(6ClW)ED]isopentylamide [SEQ ID NO: 74] and Cyclo(2,6)-6-Phenylheptanoyl-[K(Pmp)(6ClW)ED]isopentylamide [SEQ ID NO: 75].

90. A method according to claim 85, wherein the disease or disorder is related to pain transmission, anxiety, appetite, alcohol withdrawal, opiate withdrawal, epilepsy or memory.

91. A method according to claim 90, wherein the compound is an agonist or antagonist of ORL-1 receptor.

92. A method according to claim 91, wherein the compound is selected from Cyclo(6-10,11-15)-FGGFT[KARKD][KRKLD]-NH₂ (agonist) [SEQ ID NO: 76], Cyclo(6-10,11-15)-NpheGGFT[KARKD][KRKLD]-NH₂ (antagonist) [SEQ ID NO: 77], Cyclo(2-6,7-11)-Ac-T[KARKD][KRKLD]-NH₂ (antagonist) [SEQ ID NO: 78] and Cyclo(2-6,7-11)-(8-napthalen-1-yl-methyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4,5]dec-3-yl)-acetyl-[KARKD][KRKLD]-NH₂ (antagonist) [SEQ ID NO: 79].

93. Use of a compound comprising at least one alpha helical cyclic peptide, wherein each peptide comprises a sequence of five amino acid residues having a first terminal residue and a second terminal residue that are separated by an intervening sequence of three amino acid residues wherein the side chains of the first and second terminal residues are linked to each other in the manufacture of a medicament for treating or preventing a disease or condition associated with a ligand-receptor interaction that is mediated at least in part by an alpha helical domain present in the ligand or the receptor, wherein the side chains of at least some of the amino acid residues of the or each peptide are in a three-dimensional configuration that is analogous to the configuration of amino acid side chains of at least a portion of the alpha helical domain of the ligand or the receptor.

94. Use according to claim 93, wherein the disease or condition is related to an aberration in DNA transcription, RNA reverse transcription, transcriptional antitermination, apoptosis regulation,

tumor suppression, calcium homeostasis, pain transmission, memory, lipid metabolism, cholesterol homeostasis or stress response or to anxiety, appetite, alcohol withdrawal, opiate withdrawal or epilepsy.

95. Use according to claim 94, wherein the disease or condition is related to apoptosis regulation or tumor suppression.

96. Use according to claim 95, wherein the compound is selected from a BH3 domain mimetic or a p53 tumor suppressor mimetic.

97. Use according to claim 96, wherein the BH3 domain mimetic is selected from cyclo(2-6,7-11)-Y[KRELD][KMADD]F [SEQ ID NO: 57], cyclo(2-6,7-11)-V[KRQLD][KIADD]I [SEQ ID NO: 58], cyclo(2-6,7-11)-I[KAQED][KVADD]M [SEQ ID NO: 59], cyclo(2-6,7-11)-I[KAQED][KIADD]F [SEQ ID NO: 60], cyclo(2-6,7-11)-3-(4-hydroxyphenyl)-propionyl[KRELD][KMADD]-phenethylamide [SEQ ID NO: 61], cyclo(2-6,7-11)-iso-valeroyl[KRQLD][KIADD]2-methylbutylamide [SEQ ID NO: 62], cyclo(2-6,7-11)-3-methylpentanoyl-[KAQED][KVADD]-3-methylsulfanyl-propylamide [SEQ ID NO: 63], cyclo(2-6,7-11)-3-methylpentanoyl-[KAQED][KIADD]-phenethylamide [SEQ ID NO: 64], Cyclo(3,7)-LR[KMADD]F [SEQ ID NO: 65], Cyclo(3,7)-LA[KIADD]I [SEQ ID NO: 66], Cyclo(3,7)-LA[KVADD]I [SEQ ID NO: 67], Cyclo(3,7)-LA[KIADD]F [SEQ ID NO: 68], Cyclo(2,6)-7-methyl octanoyl-[KMADD]-Phenethylamide [SEQ ID NO: 69], Cyclo(2,6)-7-methyl octanoyl-[KIADD]-2-methylbutylamide [SEQ ID NO: 70], Cyclo(2,6)-7-methyl octanoyl-[KVADD]-2-methylbutylamide [SEQ ID NO: 71] and Cyclo(2,6)-7-methyl octanoyl-[KMADD]-Phenethylamide [SEQ ID NO: 72].

98. Use according to claim 96, wherein the p53 tumor suppressor mimetic is selected from Cyclo(3,7)-FM[K(Pmp)(6CIW)ED]L [SEQ ID NO: 73], Cyclo(3,7)-3-Phenylpropanoyl-M[K(Pmp)(6CIW)ED]isopentylamide [SEQ ID NO: 74] and Cyclo(2,6)-6-Phenylheptanoyl-[K(Pmp)(6CIW)ED]isopentylamide [SEQ ID NO: 75].

99. Use according to claim 94, wherein the disease or disorder is related to pain transmission, anxiety, appetite, alcohol withdrawal, opiate withdrawal, epilepsy or memory.

100. Use according to claim 99, wherein the compound is an agonist or antagonist of ORL-1 receptor.

101. Use according to claim 100, wherein the compound is selected from Cyclo(6-10,11-15)-FGGFT[KARKD][KRKLD]-NH₂ (agonist) [SEQ ID NO: 76], Cyclo(6-10,11-15)-NpheGGFT[KARKD][KRKLD]-NH₂ (antagonist) [SEQ ID NO: 77], Cyclo(2-6,7-11)-Ac-T[KARKD][KRKLD]-NH₂ (antagonist) [SEQ ID NO: 78] and Cyclo(2-6,7-11)-(8-napthalen-1-yl-methyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4,5]dec-3-yl)-acetoyl-[KARKD][KRKLD]-NH₂ (antagonist) [SEQ ID NO: 79].